REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

Claims 1-29 are currently pending. The amendments to the claims and new claims point out more particularly and claim more distinctly the subject matter of Applicants' invention. Specifically, the claims have been amended to appear in more proper American format and to correct grammatical and ideomatic errors. No prohibited new matter has been introduced by this Amendment. Applicants reserve the right to pursue in a division or continuation application any subject matter canceled by way of this Amendment without prejudice or disclaimer.

The claims have been amended to remove language which creates alternative steps for the claimed methods and to clarify the claims. New claims have been introduced herein which claim the alternative subject matter amended from the as-filed claims. Thus, basis for these amendments and new claims may be found in the specification and claims as filed.

The specification has been amended to remove a figure and to present a Brief Description of the Drawings. Basis for these amendments to the specification may be found in the specification as filed, especially on page 19, lines 1-7, page 20, line 30 to page 12, line 3 and page 24, lines 10-22.

Thus, this amendment does not introduce any new matter. Rather, it merely corrects an informalities and renders the subject matter of the claims more clear.

I. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-29 stand rejected under § 112, second paragraph, as purportedly indefinite.

Claims 1 through 3 and 26 through 28 stand rejected for the recitation for the term "such" because it is purportedly unclear whether the limitations following this phrase are part of the claimed invention. Independent claims 1 and 26 have been amended to recite, "subjecting one or more carrier starting substances to chemical operations so that said liquid". Thus, Applicants submit that this rejection has been obviated.

Claim 17 stands rejected for the recitation of the phrase "such as" because it is purportedly unclear whether the limitations following this phrase are part of the claimed invention. Claim 17 has been amended to remove the phrase "such as methacrylate" and new claim 30 has been created as depending off of claim 17 and reciting methacrylate. Thus, Applicants submit that this rejection has been obviated.

Claims 6, 7, 23 and 25 stand rejected for the recitation of the phrase "preferably". Claims 6, 7, 23 and 25 have been amended to remove the subject matter following the word "preferably". New claims 31-35 now recite the subject matter following "preferably" in the form of dependent claims. Thus, Applicants submit that this rejection has been obviated.

Claims 1, 3, 13, 27 and 28 stand rejected for the recitation of "and/or". Claims 1, 3, 13, 27 and 28 have been amended to recite "or" rather than "and/or". Thus, Applicants submit that this rejection has been obviated.

The claims stand rejected for the recitation of parentheses. The claims have been amended to remove the parentheses. Thus, Applicants submit that this rejection has been obviated.

Claims 1 through 3 and 26 through 28 stand rejected for the recitation for the phrases "to such chemical reaction" and "of such chemical". Applicants submit that the previously discussed amendments to claims 1 through 3 and 26 through 28 removing the phrase "such" obviate these rejections.

Claim 17 stands rejected for the recitation of the term "derivatives". Claim 17 has been amended to remove the term "derivatives". Thus, Applicants submit that this rejection has been obviated.

Claim 17 stands rejected for the recitation of the term "type" because it is purportedly unclear whether the limitations following this phrase are part of the claimed invention. Claim 17 has been amended to remove the term "type". Thus, Applicants submit that this rejection has been obviated.

Claims 1-3, 17, 26 and 27 stand rejected for the recitation of the term "higher" because the meets and bounds of this term are purportedly unclear. Specifically claim 1 recites "carrier matrix is provided in which the degree of saturation of said biologically active agent is higher than in said carrier starting substance(s)". The claims have been amended to recite "supersaturation" rather than that the degree of saturation is"higher". Thus, Applicants submit that this rejection has been obviated.

The claims of the present invention have also been amended in order to correct various formalities such as grammatical and idiomatic errors, and to place the claims improper U.S. format. Regarding the observations made by the Examiner

on page 4 of the outstanding Office Action, Applicants note the following. Claim 29 has been deleted by way of the present Amendment. The word "is" has been deleted from claim 27, in order to place the claim in a proper grammatical format.

II. SPECIFICATION

The disclosure stands objected to for purportedly containing a figure on page 24. The specification has been amended to remove the figure and to include a Brief Description of the Drawings section. The specification has also been amended to recite "Figure" rather than "Diagram" when referring to the Figures. Thus, objections to the specification have been obviated.

Claims 26 and 27 stand as being purportedly being incomplete for omitting essential steps. Independent claim 26 has been amended to recite method steps. Please advise us if these amendments would be acceptable to you.

Accordingly, the rejection under 35 U.S.C. § 112, second paragraph respectfully should be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. § 102

Claims 1-5, 8-14, 17 and 22-25 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Farinas *et al.* (U.S. Patent No. 5,906,830). Farinas *et al.* is cited for purportedly disclosing a method for preparing transthermal drug delivery systems containing super saturated drug reservoirs. Farinas *et al.* also purportedly discloses that an amount of drug molecules dispersed in the reservoir material at a

concentration that is greater than the solubility of the drug in the reservoir material at a room temperature to give a supersaturated drug reservoir.

For proving anticipation, "anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." Jamesbury Corp. v. Litton Industrial Products, Inc. 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). The cited reference does not describe or suggest all of the elements of the rejected claims, as discussed in greater detail below.

The present invention claims a method of creating stable, supersaturated compositions by subjecting the starting materials to chemical operations which result in a matrix capable of maintaining supersaturation. Further, independent claim 1 has been amended to recite that the supersaturated state is "obtained", rather than "obtainable".

Farinas *et al.* disclose a method of manufacture of formulations that are supersaturated with respect to the drug content. However, the method of Farinas *et al.* is based on the use of heat to create supersaturation. This technique is identical to that disclosed by Chou *et al. (J. Pharm. Sci.* (1971) 60:1281), as dicussed on page 4 of the present specification. In contrast, the present invention does not claim the dissolving of matter by increasing the temperature above the melting point to create supersaturation of the active ingredient. Rather, the present claims are directed to a method of creating stable, supersaturated compositions by subjecting the starting materials to chemical operations which result in a matrix capable of maintaining supersaturation. In the presently claimed invention, the active ingredient is present during the operations, where the solubility of the drug

decreases during the chemical operations. This characteristic is what causes the supersaturation. Farinas *et al.* fail to disclose this. Further, the products that result from the processes disclosed by Farinas *et al.* are not the same as the claimed compositions of the present invention. In the case of the present claims, the melting point depression is not utilized using polymeric mixtures.

Thus, Applicants submit that this rejection has been obviated.

Claims 1, 17-20, 23-24 and 29 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Lindahl (WO 97/00670). Lindahl is cited for purportedly disclosing a composition comprising of a polyester matrix and a biologically active agent, acyclovir. The composition of Lindahl purportedly comprises a matrix, a reaction product of citric acid and propylene glycol. The cited reference does not describe or suggest all of the elements of the rejected claims, as discussed in greater detail below. As discussed above, independent claim 1 has been amended to recite that the supersaturated state is "obtained", rather than "obtainable".

Lindahl discloses the formation of a solvent mixture based on the dilution of glass structures and citric acid glass, with a plasticizer present to prevent the precipitation of the glass forming substance, citric acid. The solvent created in Lindahl has the ability to dissolve drug substances (especially polar substances) at a level much higher than that of the starting materials. A high solubility is contraindicated for supersaturation, because if a supersaturated formulation is desired, solubility should be kept as low as possible. A formulation where the solubility of the active ingredient is 15% will require 30% of the drug to be

incorporated into the formulation, in order for it to be supersaturated two times. On the other hand, a formulation that can dissolve only 3% of the drug will be supersaturated 10 times if 30% of the active ingredient is kept in solution. The saturation level refers to the chemical activity in a specific vehicle and not to the concentration. Two supersaturated formulations having the same level of supersaturation but at different concentration levels will penetrate through biological membranes at the same rate. Thus, Lindahl fails to disclose the element supersaturation of the present claims, as amended herein.

Further, the present Office Action states that the matrix formed in Lindahl is a reaction product of the combination of citric acid and propyleneglycol. Applicants submit that Lindahl does not disclose this. In contrast, the present claims are directed to chemical operations. Prolonged exposure to heat may have an effect on the compounds included in the composition, but the disclosure of Lindahl merely recites that heating is done only for the purpose of first dissolving the citric acid and then the active drug. The heating is not done for purposes of any chemical operations and/or reactions. In the examples section of Lindahl, it is stated that when citric acid and propyleneglycol are dissolved, the temperature is lowered to 80 degrees Celcius, at which point Aciclovir is added. Lindahl goes on to recite that "After a few minutes when the aciclovir has been dissolved the temperature is lowered to room temperature". This disclosure fails to disclose or even suggest chemical operations or reactions.

Thus. Applicants submit that this rejection has been obviated.

IV. REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-7 and 22-28 stand rejected under 35 U.S.C. §103(a) as purportedly unpatentable over Farinas *et al.* The Office Action asserts that the skilled artisan would have motivated to prepare a supersaturated drug delivery reservoir according to the method disclosed in Farinas *et al.* The Office Action notes that because the presently claimed invention purportedly fails to specify what higher of saturating is to specifying is in the absence of evidence to the contrary the supersaturated drug reservoir is a supersaturated as the drug formulation of the invention.

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re* Dow Chemical Co., . . . 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the cited art of Farinas *et al.* does not suggest the methods claimed, let alone suggest that the claimed methods could be conducted with a reasonable expectation of success.

Applicants submit that the skilled artisan would not be motivated to prepare a supersaturated drug delivery reservoir according to the method disclosed in Farinas *et al.* to arrive at the claimed invention. As noted above, the method of Farinas *et al.* is based on the use of heat to create supersaturation. In contrast, the present claims are directed to a method of creating stable, supersaturated compositions by subjecting the starting materials to chemical operations which result in a matrix capable of maintaining supersaturation. In the presently claimed invention, the active ingredient is present during the operations, where the solubility of the drug decreases during the chemical operations. This element of the present claims is what causes the supersaturation. Farinas *et al.* fail to disclose or even suggest this. Further, the products that result from the processes disclosed by Farinas *et al.* are not the same as the claimed compositions of the present invention. In the case of the present claims, the melting point depression is not utilized using polymeric mixtures. Thus, the skilled artisan would not have an expectation of success at using the methods of Farinas *et al.* to arrive at the present invention.

Thus, the reference does not render obvious the invention as claimed. Accordingly, Applicants respectfully request the appropriate withdrawal of the rejection.

Claims 1-29 stand rejected under 35 U.S.C. §103(a) as purportedly unpatentable over Lindahl. The Office Action asserts that it would have been obvious to the skilled artisan at the time the invention was made to prepare the

composition of Lindahl because Lindahl's process of making the composition is similar to the mixing process of the present invention.

It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the cited art of Lindahl does not suggest the compositions and methods claimed, let alone suggest that the claimed methods could be conducted with a reasonable expectation of success.

The skilled artisan would not expect success for the following reasons. As discussed above, the solvent created in Lindahl has the ability to dissolve drug substances (especially polar substances) at a level much higher than that of the starting materials. A high solubility is contraindicated for supersaturation, because if a supersaturated formulation is desired, solubility should be kept as low as possible. Thus, Lindahl fails to disclose, or even to suggest, the element of supersaturation of the present claims.

Further, Lindahl merely recites that heating is done only for the purpose of first dissolving the citric acid and then the active drug. The heating is not done for purposes of any chemical operations and/or reactions. This disclosure fails to disclose or even suggest chemical operations or reactions. Rather, it teaches that the purpose is to keep the amount of reaction products as low as possible. Upon reading the teaching of Lindahl that to goal is to keep reaction products as low as possible, the skilled artisan would not be motivated to use the process of Lindahl for the purposes of chemical reactions, as in the claimed invention.

Further, the present invention has unexpectedly overcome the difficulty with the stabiluty of supersaturation of drugs. The present invention has overcome this

difficulty, and the product remains stable for months. In contrast, the product disclosed by Lindahl has a much shorter stability.

Thus, the reference does not render obvious the invention as claimed. Accordingly, Applicants respectfully request the appropriate withdrawal of the rejection.

V. REJECTIONS UNDER DOUBLE PATENTING

Claim 1 is provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1 and 2 of copending U.S. Patent Application No. 09/700,176. Applicants respectfully ask the Examiner to hold this rejection in abeyance until one of the patent applications issues as a patent.

Claims 1-29 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of copending U.S. Patent Application No. 09/700,176. Applicants respectfully ask the Examiner to hold this rejection in abeyance until one of the patent applications issues as a patent.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: July 25, 2002

Attachment to Amendment and Reply

Marked-Up Copy

Page 20, Paragraph Beginning at Line 30

The measured permeation rates are depicted in the enclosed [Diagram 1] Figure 1.

Page 20, Paragraph Beginning at Line 33 through Page 21, Paragraph Beginning at Line 1

[Diagram 1] Figure 1 shows that a considerably higher Permeation rate is obtained in the compositions B_1 and B_2, as compared to any one of the compositions A or C. This increased permeation rate is in turn clear evidence that the thermodynamic potential of metronidazole is significantly higher in the compositions B_1 and B_2 in comparison with any one of the compositions A_0 or C. Here, it is important to note that the compositions A_0 and B are initially the same.

Page 21, Paragraph Beginning at Line 13

A Franz diffusion cell as disclosed above was used under conditions similar to those of example 1, unless otherwise noted. Permeation rate experiments were performed for 21 h. As a reference, the permeation rate from the saturated composition C in example 1 was determined to be 46 μg per 21 h in a Franz diffusion cell experiment, as depicted in [Diagram 1] Figure 1. The experiments

were all analysed by use of spectrophotometry. The results are depicted in [diagram 2] Figure 2.

Page 24, Paragraph Beginning at Line 15

[As depicted above, Diagram 2] Figure 2 shows that the chemical operation subjected to the compositions X1-X4 upon manufacturing of the compositions Y1-Y4 resulted in an increased thermodynamic potential of metronidazole, as is directly evidenced through the increased permeation rate. The permeation rate for a Y composition has increased approximately 40% in comparison with its corresponding X composition.

Attachment to Amendment and Reply

Marked-up Claims 1-29

1. (Amended) A biologically active composition comprising:

a biologically active agent to be released therefrom, [said] wherein the biologically active [agent being] composition is dissolved [and/or] or dispersed in a carrier [therefor], wherein said carrier is a liquid [and/or] or solid non-crystalline matrix in which said biologically active agent is present in a supersaturated state, [said] and wherein the supersaturated state is obtained [being obtainable] by subjecting one or more carrier starting [substance(s)] substances to [such] chemical [operation(s)] operations so that [said] the liquid or [and/or] solid non-crystalline increases until a supersaturated carrier matrix is provided [in which the degree of saturation of said biologically active agent is higher than in said carrier starting substance(s)], the biologically active agent being added before [said] the chemical [operation(s) has (have)] operations have been completed.

2. (Amended) The [A] composition according to claim 1, wherein the [said higher degree of saturation] supersaturation is the result of such chemical [operation(s)] operations that the solubility of the biologically active agent in said matrix is lower than the solubility thereof in said carrier starting substance[(s)].

3. (Twice Amended) The [A] composition according to claim 2, wherein said [higher degree of saturation] supersaturation is the result of [such] chemical

[operation(s)] operations such that the degree of dissociation, aggregation [and/or] or degree of protonation of the biologically active agent is different from the degree of dissociation, aggregation [and/or] or degree of protonation of [said] the agent in [said] the carrier starting substance[(s)].

4. (Twice Amended) The [A] composition according to claim 1, wherein [said] the biologically active agent is added before [said] the chemical [operation(s) has (have)] operations have been initiated.

5. (Twice Amended) The [A] composition according to claim 1, wherein [said] the biologically active agent is added at a predetermined point of time after [said] the chemical [operation(s) has (have)] operations have been initiated, the composition thus obtained then being further subjected to [said] the chemical [operation(s)] operations.

6. (Twice Amended) The [A] composition according to claim 5, wherein [said] the predetermined point of time is from 1 minute to 6 months[, preferably from 0,5 hours to 4 months] after [said] the chemical [operation(s) has (have)] operations have been initiated.

7. (Amended) The [A] composition according to claim 6, wherein the composition is further subjected to [said] the chemical [operation(s)] operations for a

time period of about from 1 minute to 6 months[, preferably from 0,5 hours to 4 months].

8. (Twice Amended) The [A] composition according to claim 1, wherein [said] the starting substance[(s)], or said formed non-crystalline matrix, [act(s)] acts as a solvent or dispersing medium.

9. (Twice Amended) The [A] composition according to claim 1, wherein [said] the biologically active agent is added as a solid [and/or] or liquid which is subsequently dissolved in [said] the carrier.

10. (Twice Amended) The [A] composition according to claim 1, wherein [said] the biologically active agent is added in the form of a solution or dispersion.

11. (Twice Amended) The [A] composition according to claim 1, wherein [said] the biologically active agent is added above or around room temperature.

12. (Twice Amended) The [A] composition according to claim 1, wherein [said] the chemical [operation(s)] operations comprise one or more chemical reactions.

13. (Amended) The [A] composition according to claim 12, wherein [said] the chemical [reaction(s)] reactions comprise etherifying, esterifying, hydrolysis, substitution, addition, elimination, oligomerising [and/or] or polymerising reactions.

14. (Amended) The [A] composition according to claim 13, wherein [said] the chemical [reaction(s) is (are)] reactions are selected and performed so as to provide optimal delivery rate of [said] the biologically active agent.

15. (Twice Amended) The [A] composition according to claim 1, wherein [said] the chemical [operation(s) involve(s)] operations involve subjecting [said] the carrier starting substance[(s)] to a temperature of from around -50°C to around 300°C[, preferably around 0-150°C].

16. (Twice Amended) The [A] composition according to claim 1, wherein [said] the chemical [operation(s) is (are)] operations are conducted for a time period of from 1 minute to 6 months[, preferably from 0,5 hours to 4 months].

17. (Twice Amended) The [A] composition according to claim 1, wherein [said] the carrier starting substance, or mixture of two or more difference carrier starting substances, is selected from the group consisting of monomers, acids, [such as mono-, di- or triacids or higher acids,] alcohols, [including mono-, di- or triols,] ketones, aldehydes, amines, amides, anhydrides, lactides, glycolides, saccharides [and derivatives thereof], acrylic or acrylamide [type] compounds[, such as methyl

methacrylate], monomers of PEO-diacrylate, cyanoacrylate, acrylate saccharides[, including acrylate starch], acrylate lactate, acrylate glycolate, isocyanates, ethylene oxide, propylene oxide, pyrrolidone, PEO-diacrylate, ethylene-vinyl acetate, monomers of organic siloxanes, and oligomers, polymers [or] and prepolymers thereof.

18. (Amended) The [A] composition according to claim 17, wherein the acid is a monomeric acid and the alcohol is a monomeric alcohol, [said] wherein the non-crystalline matrix [comprising] comprises an ester [and/or] or polyester thereof.

19. (Amended) The [A] composition according to claim 18, wherein [said] the monomeric acid is citric acid.

20. (Twice Amended) The [A] composition according to claim 18, wherein [said] the monomeric alcohol is propylene glycol.

21. (Twice Amended) The [A] composition according to claim 1, which consists of one liquid or solid phase only.

22. (Twice Amended) The [A] composition according to claim 1, wherein the biologically active agent is a pharmaceutically active agent.

23. (Twice Amended) The [A] composition according to claim 22, wherein the pharmaceutically active agent is selected from the group consisting of guanosides, corticosteroids, psychopharmaceutical hormones, oxicams, peptides, proteins, antibiotics, antivirals, antimicrobials, anticancer agents, antifungals, oestrogens, antiinflammatory agents, neuroleptic agents, melanocyte stimulants and gland stimulants[, preferably stimulators of sebaceous and pilo-sebaceous glands,] and agents with an effect on mast cell secretion.

24. (Amended) The [A] composition according to any one of claims 22 and 23 for use as a medicament.

25. (Twice Amended) The [A] composition according to claim 1, wherein the composition is applied topically [for topical, preferably dermal application] to a mammal[, preferably man].

26. (Amended) A method for the preparation of a biologically active composition comprising:

dissolving or dispersing the [a] biologically active [agent] composition [dissolved [and/or dispersed] in a carrier [therefor], and

subjecting [wherein] a carrier starting substance, or a mixture of two or more different carrier starting substances, [is (are) subjected] to [such] chemical [operation(s)] operations so that a liquid [and/or] or solid non-crystalline carrier matrix is formed, in which the degree of saturation of [said] the biologically active

agent is increased until supersaturated [higher than is said carrier starting substance(s),] said biologically active agent [being] is added before [said] the chemical [operation(s) has (have)] operations have been completed and in an amount such that a supersaturated state is obtained.

27. (Twice Amended) The [A] method according to claim 26, wherein [said] the composition [is] comprises a biologically active agent to be released therefrom,

[said] wherein the biologically active agent [being] is dissolved [and/or] or dispersed in a carrier [therefor],

wherein [said] the carrier is a liquid [and/or] or solid non-crystalline matrix in which [said] the biologically active agent is present in a supersaturated state, [said] the supersaturated state being obtainable by subjecting one or more carrier starting substance[(s)] to [such] chemical [operation(s)] operations so that [said] the liquid [and/or] or solid non-crystalline carrier matrix is provided in which the degree of saturation of [said] the biologically active agent is increased until supersaturated [higher than in said carrier starting substance(s)], the biologically active agent being added before [said] the chemical [operation(s) and (have)] operations have been completed, and

wherein [said] the supersaturation [higher degree of saturation] is the result of [such] chemical [operation(s)] operations such that the solubility of the biologically active agent in [said] the matrix is lower than the solubility thereof in [said] carrier [staring] starting substance[(s)].

28. (Amended) The [A] composition according to claim 2, wherein [said higher degree of saturation] the supersaturation is the result of [such] chemical [operation(s)] operations such that the degree of dissociation, aggregation [and/or] or degree of protonation of the biologically active agent is different from the degree of dissociation, aggregation [and/or] or degree of protonation of [said] the agent in [said] the carrier starting substance[(s)].

29. (Amended) The [A] composition according to claim 19, wherein [said] the monomeric alcohol is propylene glycol.